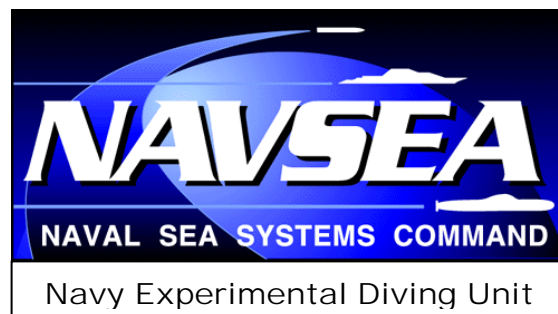


Navy Experimental Diving Unit  
321 Bullfinch Rd.  
Panama City, FL 32407-7015

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## EFFECTS OF BREATHING RESISTANCE ON RESTING VENTILATORY SENSITIVITY TO CO<sub>2</sub>



Authors: B. Shykoff, Ph.D.  
D. Warkander, Ph.D.

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14. ABSTRACT Carbon dioxide partial pressure (PCO <sub>2</sub> ) is normally tightly controlled in blood and tissues. However, if the respiratory controller also protects the respiratory muscles by optimizing for their loading, ventilatory response to CO <sub>2</sub> may be damped when resistance to breathing increases. This has been observed during heavy exercise with resistive breathing loads. Also observed has been a lack of correlation between PCO <sub>2</sub> at the end of the heavy exercise and resting ventilatory sensitivity to CO <sub>2</sub> . We hypothesized that the disparity was caused by a change in the effective ventilatory sensitivity to CO <sub>2</sub> with resistance in the breathing circuit. In 16 Navy divers, ventilatory sensitivity to CO <sub>2</sub> was measured at rest using Read's method. Measurements were made with the basic rebreathing circuit and with moderate resistance on the inspiratory, expiratory, or both sides. The resistance elements were designed to generate work of breathing per tidal volume of 1 kPa when minute ventilation was 100 L/min. Resistance caused no systematic change in ventilatory sensitivity. However, the distribution of sensitivities, while not different from that for the general population, included some divers with very low values. Those divers may be at risk of hypercapnia, but a correlation between resting dry measurements and in-water exercise measurements cannot be established.					
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## INTRODUCTION

Normal physiological responses provide tight control of carbon dioxide partial pressure ( $\text{PCO}_2$ ) in blood and tissues to maintain acid-base balance. The peripheral and central chemoreceptors sense  $\text{PCO}_2$  and pH. Pulmonary ventilation adjusts to wash out or retain  $\text{CO}_2$  as appropriate. The healthy, unimpeded respiratory system maintains arterial  $\text{PCO}_2$  at  $40 \pm 2$  Torr at rest or during light to moderate exercise. Arterial  $\text{PCO}_2$  normally is lower during heavy exercise when lactic acid must be cleared.

$\text{CO}_2$  homeostasis may be disrupted by the inability to ventilate the lungs sufficiently or by a change in respiratory drive from decreased chemoreceptor function. Ventilatory response to  $\text{CO}_2$  may be damped even at manageable levels of work of breathing and with normal chemoreceptor sensitivity if physiological optimization attempts to protect the respiratory muscles by optimizing for both chemical ( $\text{CO}_2$ ) and energy (work of breathing) loading.<sup>1</sup>

Divers and others who use breathing apparatus have increased ventilatory requirements because inspired air may contain  $\text{CO}_2$ , either trapped from the previous exhalation (dead space) or in the gas that is supplied. All users of breathing apparatus also have potentially compromised ability to breathe; resistive pressure drops in breathing gear create extra energy needs characterized as external work of breathing. For divers, elevated gas density under water increases the internal work of breathing. Inspired  $\text{CO}_2$  and elevated work of breathing increase the risk of disturbed  $\text{CO}_2$  homeostasis. This work examined the possibility that apparent respiratory drive would decrease with mildly increased external work of breathing.

Research at the Navy Experimental Diving Unit (NEDU) has shown that ventilation during heavy exercise in the laboratory is considerably lower and that end-tidal  $\text{PCO}_2$  is higher with resistance in the breathing circuit than without it.<sup>2, 3</sup> Work has continued to investigate relationships among ventilation,  $\text{PCO}_2$ , and resistance during heavy exercise in divers submerged in shallow water.<sup>4</sup> Other investigators also have shown that the ventilatory increase with exercise is blunted by resistance.<sup>5, 6</sup> Subjects who inhale gas containing  $\text{CO}_2$  increase minute ventilation ( $\dot{V}_E$ ) both at rest and during mild to moderate exercise when the resistance of their breathing circuit is minimal.<sup>7-12</sup> However, subjects show a much smaller increase in  $\dot{V}_E$  with inhaled  $\text{CO}_2$  at rest and during exercise with greater resistance in the breathing circuit.<sup>14, 15</sup> Subjects at rest breathing elevated inspired  $\text{CO}_2$  moderate increases in  $\dot{V}_E$  to match inspiratory WOB to  $P_{\text{ET}}\text{CO}_2$  across a range of resistances.<sup>14</sup>

The currently most-accepted approach to determine ventilatory sensitivity to  $\text{CO}_2$  is the rebreathing method in which a subject rebreathes a volume of test gas slightly larger than vital capacity. The initial gas composition is 7%  $\text{CO}_2$  and 93%  $\text{O}_2$ , and rebreathing time is about 4 minutes.<sup>16, 17</sup> Equilibrium among mixed venous blood, arterial blood, and lung and bag gas is established within a few breaths, after which both peripheral and central chemoreceptors are usually considered to be exposed simultaneously to nearly

the same  $PCO_2$  as that in the lungs. Accumulation of  $CO_2$  in blood and gas during the rebreathing depends only on metabolic production of  $CO_2$  and not on pulmonary ventilation. Resting ventilatory sensitivity to  $CO_2$  is defined as the increase in  $\dot{V}_E$  with increasing  $PCO_2$ .

In NEDU's <sup>2,3</sup> and other <sup>18</sup> previous work,  $PCO_2$  at the end of heavy exercise was uncorrelated with resting ventilatory sensitivity to  $CO_2$  for the same subjects. However, other investigators report a correlation.<sup>19</sup> We hypothesized that the lack of correlation in our previous work might have been caused by alterations in apparent chemoreceptor responses by resistance. Indeed, some reports in the literature suggest that resistive breathing circuits may decrease even resting ventilatory response to  $CO_2$ .<sup>14, 15, 20, 21</sup> Thus, resting ventilatory sensitivity to  $CO_2$  was measured with and without resistances in the breathing circuit.

This work was done in conjunction with a larger study of exercise endurance and ventilatory parameters with and without breathing resistance and inspired  $CO_2$ ,<sup>4, 22, 23</sup> but only the ventilatory sensitivity measurements are reported here. The in-water study is described in full in NEDU TR 12-xx.<sup>23</sup>

## METHODS

### GENERAL

Ventilatory sensitivity to  $CO_2$  was measured as one part of NEDU protocol number 13-11/40052, "CO<sub>2</sub> and UBA-like Resistance Underwater: CO<sub>2</sub> Retention, Cognition, and Exercise Endurance."<sup>22</sup> The Institutional Review Board at NEDU had approved the protocol.

A total of sixteen qualified U.S. Navy divers from NEDU and NEDU Reserve Unit Great Lakes gave written informed consent and participated in the study. Diver characteristics are listed in Table 1.

**Table 1.** Subject characteristics. Median values, with minimum to maximum in parentheses.

	16 men
<b>Age (years)</b>	34 (23–51)
<b>Height (cm)</b>	178 (170–185)
<b>Body mass (kg)</b>	86 (60–118)

Each subject completed four measurements of ventilatory sensitivity to  $CO_2$  with differing resistances in the system: added inspiratory resistance, added expiratory resistance, both resistances added, or no additional resistance. Measurements were made using the standard rebreathing (Read's) method.<sup>16, 17</sup> Resistance conditions were

presented with varied first condition and in different sequence to different subjects, but without formal randomization.

In the underwater study,<sup>23</sup> in brief, the divers pedaled underwater cycle ergometers at nominally 85% of maximum oxygen uptake rate until voluntary termination or to a predetermined end tidal PCO<sub>2</sub>. The open-circuit breathing system sometimes included resistance elements designed to mimic a closed-circuit underwater breathing apparatus. CO<sub>2</sub> retention from those experiments was compared to the sensitivity measurements.

## EXPERIMENTAL DESIGN AND ANALYSIS

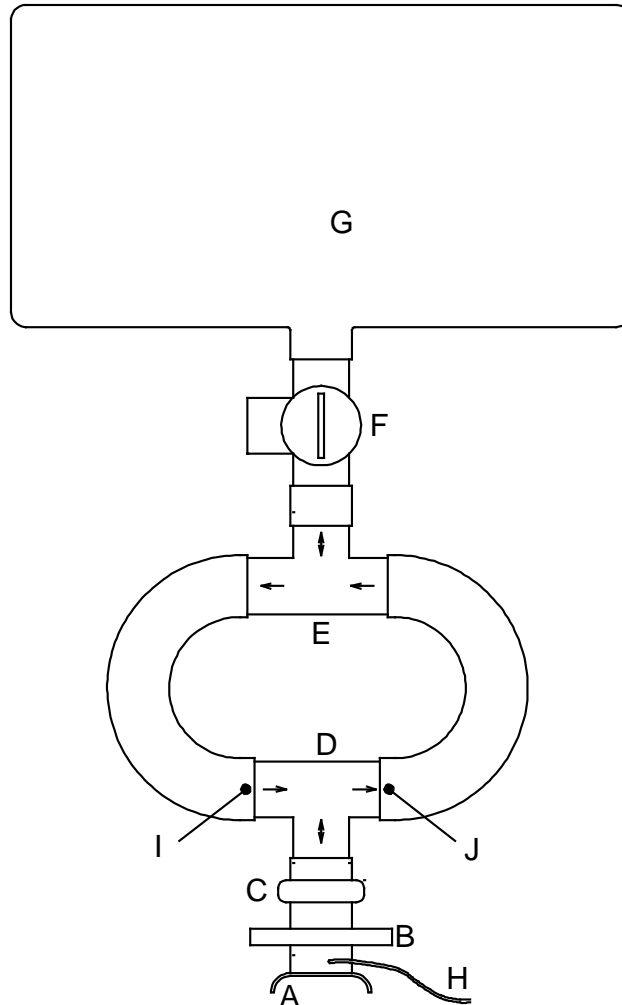
Ventilatory sensitivity to CO<sub>2</sub> was obtained as the slope of  $\dot{V}_E$  as a function of mixed rebreathing bag PCO<sub>2</sub> for each of the resistance conditions. For some subjects the relationship was not a single straight line, but was piecewise linear, with one slope at moderately elevated and another at highly elevated PCO<sub>2</sub>. Thus, two values of sensitivity were computed. Sensitivities were compared to published population parameters<sup>16</sup> and within subjects across resistance conditions. Minute ventilation ( $V_E$ ) when PCO<sub>2</sub> in the rebreathing system was 60 Torr (8.4% CO<sub>2</sub> on a dry gas basis) was also read as an index of ventilatory sensitivity.

## EQUIPMENT AND INSTRUMENTATION

A three-L calibrated syringe (Cosmed USA, Chicago, IL) was used to transfer measured volumes of test gas from a K-bottle and regulator to a 25-L rebreathing bag. Test gas was 7% CO<sub>2</sub> in a background of O<sub>2</sub>.<sup>16</sup>

The test apparatus is diagrammed in Figure 1. The rebreathing bag was connected to a mouthpiece using two two-way non-rebreathing valves (Hans Rudolph 2700) and a three-way, large bore stopcock (Hans Rudolph 2100, Hans Rudolph, Kansas City, MO) to create a one-way flow pattern through the system (Figure 1). A sample line to a sector mass spectrometer (MGA 1100, Marquette) was inserted directly into the mouthpiece. A particulate filter was placed between the mouthpiece and the first one-way valve to protect the system from droplets, viruses and bacteria. The type of particulate filter used (DCII, nSpire medical) is rated to block 99.9% of viruses and bacteria, and has a dead space of 70 mL and resistance to air flow of 0.54 cm H<sub>2</sub>O/L/s at 14 L/s.

The particulate filter connected directly to a turbine flow meter (Cosmed k4b2), which was then connected to the common port of one of the one-way valves. Turbine measurements are independent of gas viscosity and, at atmospheric pressure, of gas density. The k4b2 turbine turns once for every 24 mL and provides three pulses per revolution to detect flows between 0.03 and 20 L/s,  $\pm 2\%$ . The flow meter resistance is specified as  $< 0.7$  cm H<sub>2</sub>O/(L/s) at 12 L/s. Software converts the pulses to breath-by-breath minute ventilation.



**Figure 1.** Schematic of the test apparatus. A: mouthpiece, B: particulate filter, C: flow meter, D, E: two-way non-rebreathing (routing) valves, F: three-way stopcock, G: rebreathing bag, H: sample line to mass spectrometer, I: placement of any inspiratory resistor, J: placement of any expiratory resistor. Arrows indicate direction of gas flow.

The Hans Rudolph 2700 routing valves have nominal pressure drop of 0.7 and 0.8 cm H<sub>2</sub>O at 100 L/min for inspiration and expiration respectively. Large-bore (1.5" [38 mm] i.d.) tubing connected the two sides of that routing valve to another similar valve, the common port of which was connected to the common port of a three-way stopcock (Hans Rudolph 2100). The mouthpiece could thus be connected to room air or to the rebreathing bag by turning the stopcock. The resistance of the three-way stopcock is nominally 0.11 or 0.24 cm H<sub>2</sub>O at 100 L/min in the through (rebreathing) position and the 90° position (room air connection), respectively. When the resistances were added to the system, plugs with holes 0.56" (14.2 mm) in diameter were inserted into the inspiratory and/or expiratory side of the routing valve nearer the mouthpiece. The plugs

are the inspiratory resistance elements from the dry exercise study done at NEDU<sup>2,3</sup> and match the total inspiratory resistance of the test pool respiratory monitoring system (TPRMS) under the higher resistance condition. (The TPRMS was used during in-water exercise testing.) The resistances provide a measured pressure drop of 1.7 cm H<sub>2</sub>O at 100 L/min, and measured work of breathing at minute ventilation of 100 L/min of 1 kPa each.

The subject's minute ventilation during each test was measured using the Cosmed flow meter and k4b2 system for breath-by-breath values. Volumes are expressed at body temperature, ambient pressure, and saturated with water vapor (BTPS). CO<sub>2</sub> fraction at the mouth was measured using the mass spectrometer as fraction of CO<sub>2</sub> in the dry gas, and sampled and stored at 100 Hz using Labview (National Instruments, Austin, TX). The k4b2 breath-by-breath peak expired and mixed inspired CO<sub>2</sub> signals, provided by a micro near infrared instrument, although not accurate with the high oxygen gas,<sup>24</sup> were used to help determine when the gas was mixed between lung residual and bag. This information helped to synchronize the mass spectrometer signal to the Cosmed flow meter signal. The average mass spectrometer output after mixing and equilibration was a linear function of time. Linear regression was used to transfer the mass spectrometer readings to the breath-by-breath files.

## PROCEDURES

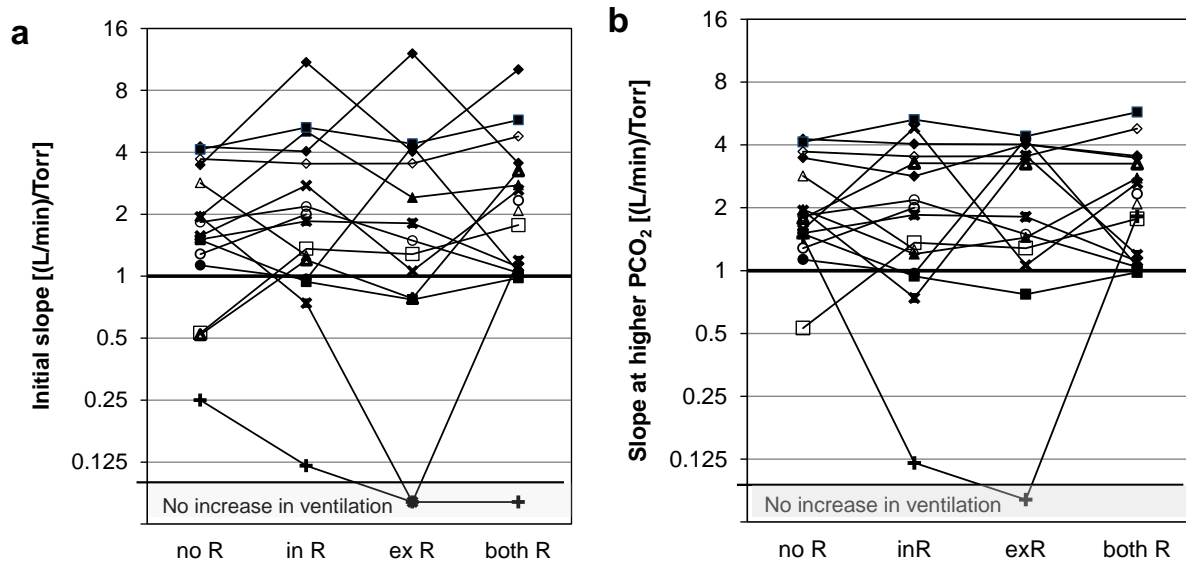
Before each test, the rebreathing bag was rolled to empty it completely. It was then supplied with a volume of test gas that was about one liter larger than the subject's estimated vital capacity.<sup>16</sup> The subject sat in a chair facing a table on which the breathing circuit rested. He donned a nose clip and began to breathe room air through the circuit. Once flow signals were detected with the Cosmed flow meter, the subject was asked to exhale to residual volume. On his indication that expiration was complete, the stopcock was turned to connect the rebreathing bag and the subject took three large breaths to mix the test gas with the residual gas in his lungs and in the system. After mixing the gas, the subject relaxed and breathed without further voluntary control. Subjects were instructed to drop the mouthpiece at any time if they felt the need. Testing continued for a maximum of four minutes<sup>16</sup> or until the PCO<sub>2</sub> in the system reached 70 Torr. Data collection was discontinued as the subject came off the mouthpiece to breathe room air.

Subjects remained seated for a few minutes until the immediate effects of breathing high PCO<sub>2</sub> had dissipated. Tests for different resistance conditions were separated by at least 10 minutes.<sup>25</sup>



## RESULTS

The ventilatory sensitivity for all subjects and all conditions is shown in Figure 2, with the initial rebreathing period values in Figure 2a and the later rebreathing period values in Figure 2b. For the condition without added resistance in the circuit, three subjects exhibited initial ventilatory sensitivity below 1 (L/min)/Torr (“low sensitivity”), two subjects had sensitivities above 4 (L/min)/Torr (“high sensitivity”), and twelve were between 1 and 4 (L/min)/Torr (“expected sensitivity”) (Figure 2a). One of the subjects with low sensitivity became normally responsive [slope 1.8 (L/min)/Torr] once PCO<sub>2</sub> climbed above 58 Torr



**Figure 2.** Measured slopes, all subjects, all conditions, a) for the initial rebreathing period once PCO<sub>2</sub> in the well-mixed system began to rise monotonically; b) later in the rebreathing period. The vertical axis has been log-transformed to spread the values. The heavy line marking slope = 1 (L/min)/Torr represents the lower bound of expected sensitivities. The upper bound of expected slopes is 4 (L/min)/Torr. The grey zone at the bottom of the figure indicates absence of response. Symbols repeat, but each set of connected symbols shows data for one person, and the symbols are consistent between panels a and b. “R” stands for resistance, and “in” and “ex” for “inspiratory” and “expiratory”.

With inspiratory resistance, the numbers were similar to the condition without added resistance: four subjects with low initial sensitivity, nine subjects with expected sensitivity, and three subjects with high sensitivity. One subject showed an increase in sensitivity from 1.2 to 3.2 (L/min)/Torr when PCO<sub>2</sub> climbed past 59 Torr. Two subjects with high sensitivity showed a slower increase in ventilation with PCO<sub>2</sub> after ventilation reached 40 L/min and 60 L/min respectively.

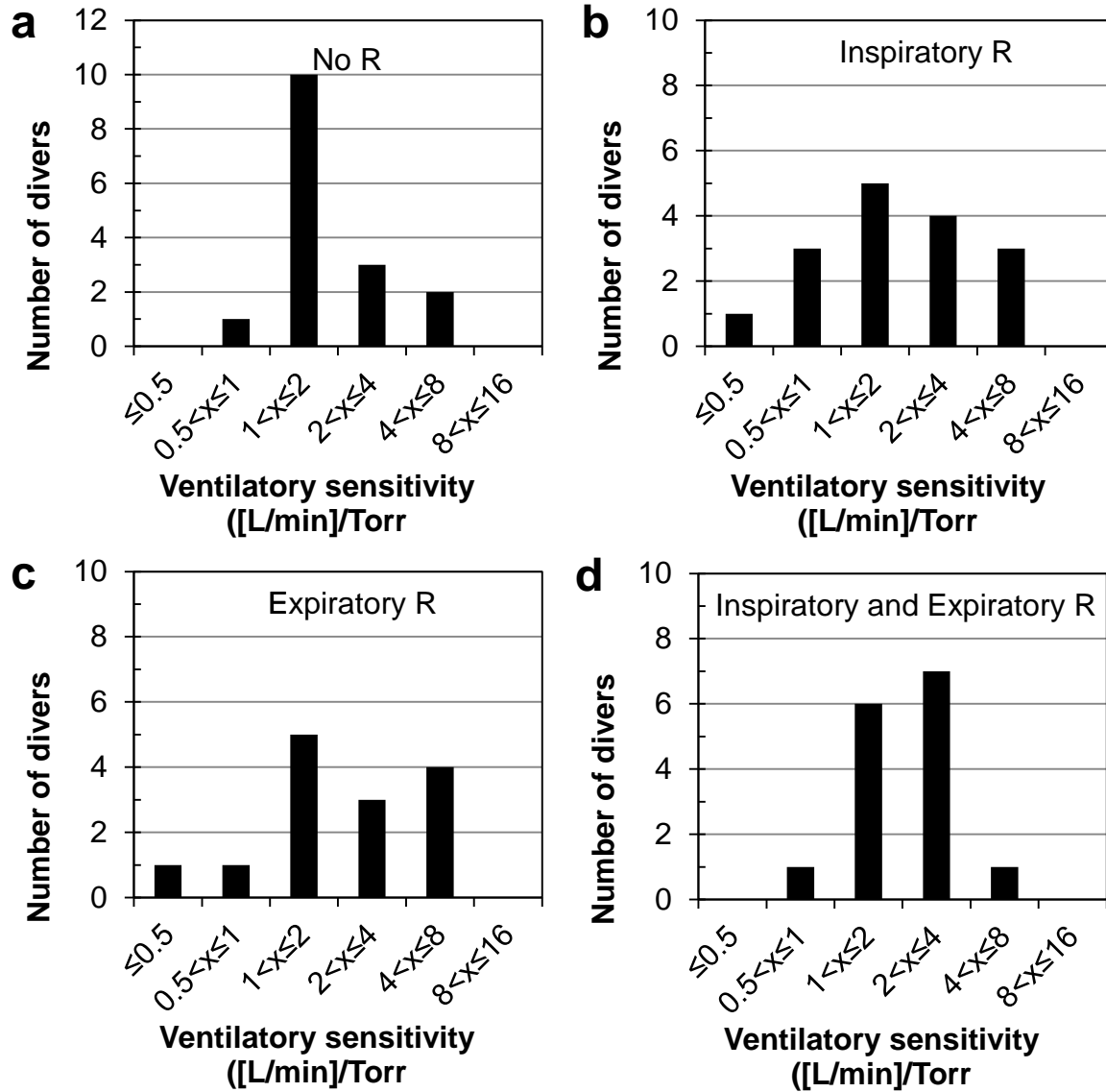
With only expiratory resistance added, the four subjects with initially low sensitivity included two who **decreased** ventilation as they initially accumulated CO<sub>2</sub> in the rebreathing circuit. One of them increased ventilation normally once PCO<sub>2</sub> reached 63 Torr [slope 3.6 (L/min)/Torr]. Two subjects who showed expected sensitivity in all other conditions are missing from the record of expiratory resistance because of experimenter error.

Figure 2 also shows the effects of resistance on the ventilatory sensitivity for individual subjects. Of the three subjects with low initial sensitivity in the absence of extra resistance, one had expected sensitivity for all conditions with added resistance; one had expected sensitivity for either inspiratory resistance alone or both resistances but low sensitivity with expiratory resistance alone; and one had low to absent initial ventilatory response to CO<sub>2</sub> in the presence of inspiratory resistance (Fig. 2a). That subject showed expected slopes of ventilation with increasing PCO<sub>2</sub> at high PCO<sub>2</sub>, but only without added resistance or with both resistances (Fig. 2b). The slopes were 1.4 (L/min)/Torr above 55 Torr without added resistance, and 1.8 (L/min)/Torr above 54 Torr with both resistances.

Three subjects had notable increases in initial sensitivity — approximately a tripling of the slope of ventilation against PCO<sub>2</sub> — one with inspiratory resistance alone, one with expiratory resistance alone, and one with inspiratory and both resistances (Fig. 2a), but the increases were not sustainable for the entire four minutes of rebreathing (Fig. 2b). One subject showed expected sensitivity without added resistance but no response to CO<sub>2</sub> with expiratory resistance present (Figs. 2a, b). That subject showed delayed responses with no added resistance and with both resistances present, as did one other when expiratory resistance was present (Figs. 2a, b).

With both added resistances, only two subjects initially had lower ventilatory sensitivity than expected. One of them showed no sensitivity until PCO<sub>2</sub> reached 52 Torr, after which his ventilation increased at a normal rate of 1.8 (L/min)/Torr. The response of one of the two subjects with high sensitivity was damped after ventilation reached 70 L/min.

Ventilatory sensitivity to CO<sub>2</sub> is not normally distributed. It is skewed with the mode at the low-value side and a long tail to higher values. This approximates a log normal distribution (the logarithm of the values is normally distributed). Figure 3 shows the distribution of sensitivities at the end of the rebreathing periods accordingly with the categories representing a doubling of sensitivity, that is, in a logarithmic representation.

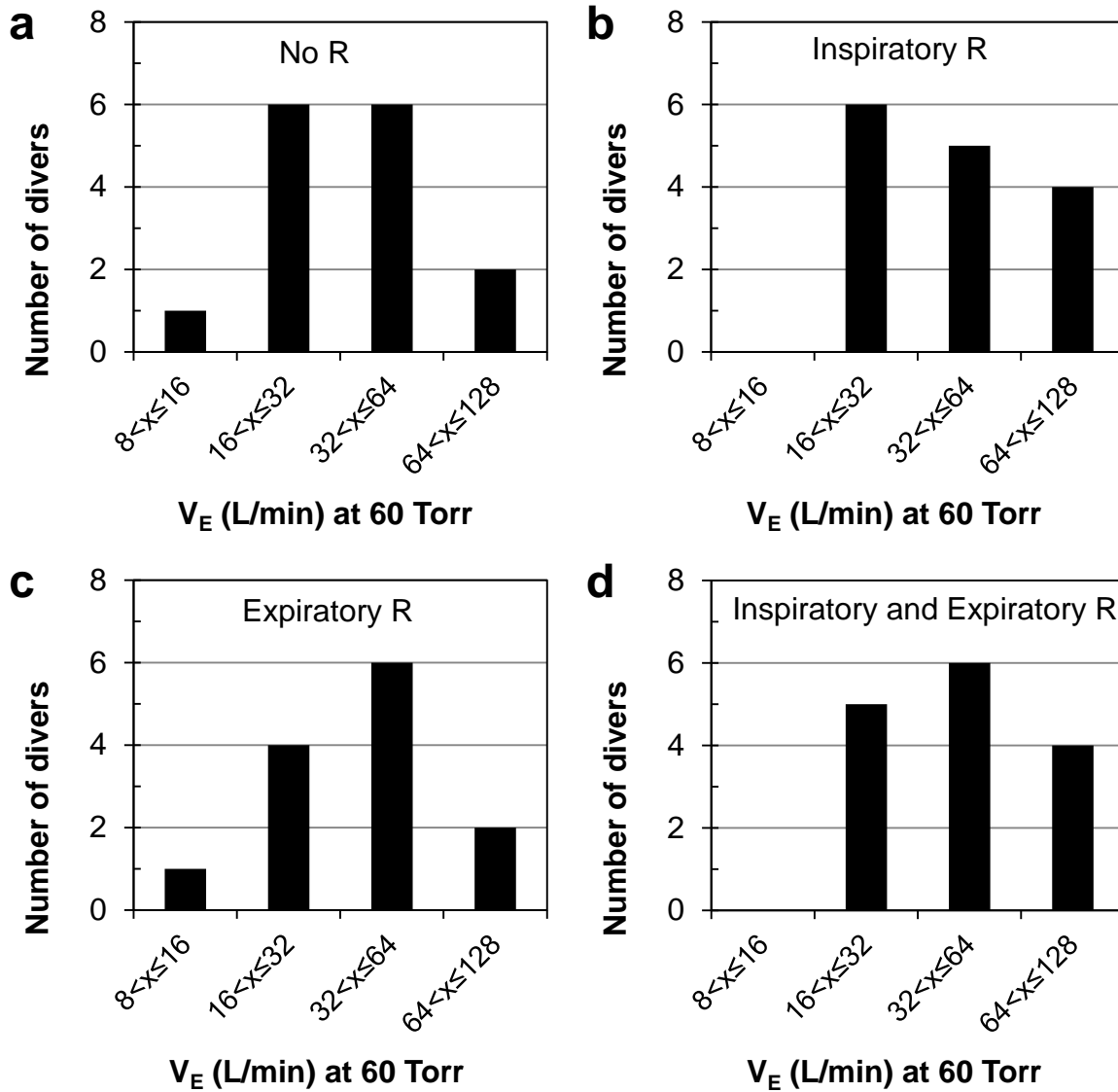


**Figure 3.** Ventilatory sensitivity distribution at the end of rebreathing, a) no added resistance, b) inspiratory resistance, c) expiratory resistance, d) both inspiratory and expiratory resistance. Each category represents a doubling of sensitivity relative to the one to its left, commensurate with a logarithmic scale. “R” means resistance.

Repeated measures analysis of variance of log-transformed data showed no significant differences in mean responses across conditions ( $p > 0.19$ ). There was no significant effect ( $p > 0.8$ ) of the order in which the tests were performed.

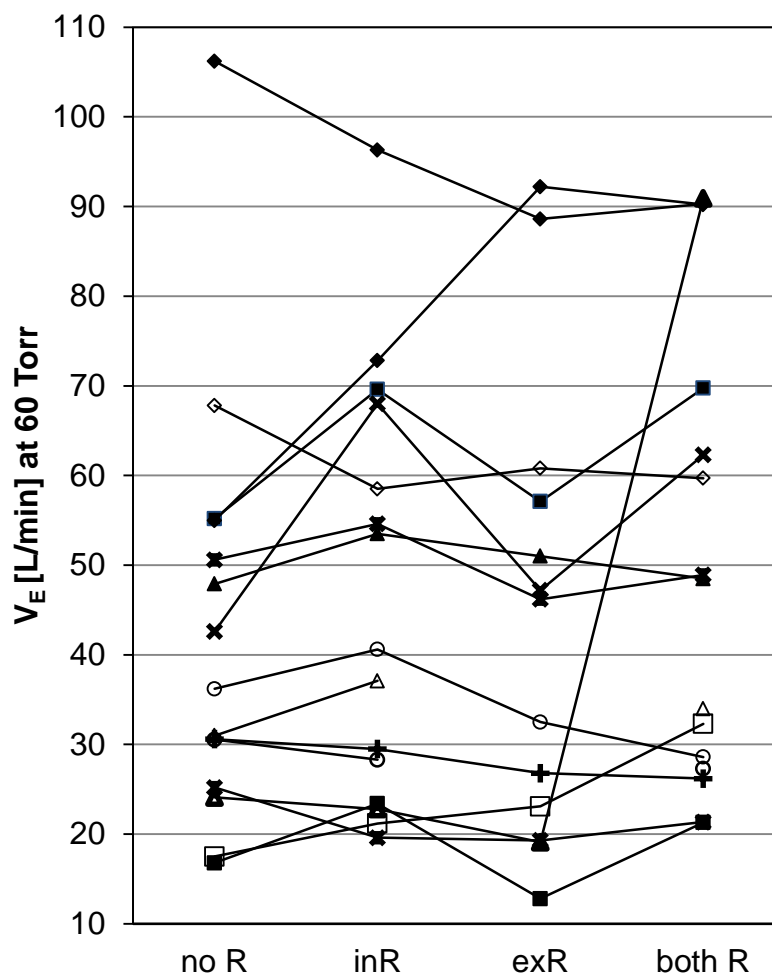
Because of the different  $PCO_2$  thresholds for increased ventilation across subjects, the slopes of ventilation against  $PCO_2$  do not fully indicate effective ventilatory response to

PCO<sub>2</sub>. Another measure of ventilatory sensitivity is the ventilation at a fixed PCO<sub>2</sub> during rebreathing.



**Figure 4.** Distribution of minute ventilation when PCO<sub>2</sub> in the system was between 58 and 60 Torr a) no added resistance, b) inspiratory resistance, c) expiratory resistance, d) both inspiratory and expiratory resistance. Each category represents a doubling of minute ventilation relative to the one to its left, commensurate with a logarithmic scale. “R” means resistance.

The distribution of ventilation when PCO<sub>2</sub> was 58 to 60 Torr is given in Figure 4.  $\dot{V}_E$  for different individuals at this PCO<sub>2</sub> ranged from 11 to 106 L/min across all conditions. No systematic differences in ventilation with resistance were observed in this small sample.



**Figure 5.**  $\dot{V}_E$  at 60 Torr, all subjects, all conditions. Symbols repeat, but each set of connected symbols shows data for one person, and the symbols are consistent between Figures 2 and 5. “R” stands for resistance, and “in” and “ex” for “inspiratory” and “expiratory”.

The range of ventilatory response is presented in Figure 5. Note the mild decrease in  $\dot{V}_E$  with resistance for some subjects, notably the two with the highest ventilation in the absence of resistance, but the large increases in ventilation with added resistance for two subjects.

Ventilatory sensitivity later in the rebreathing period was correlated with  $\dot{V}_E$  at 60 Torr as it must be given the interrelationship of the data. The correlation coefficients were 0.78 for no added resistance, 0.70 with inspiratory resistance, 0.57 with expiratory resistance, and 0.70 with both added resistances. No correlations were found between resting ventilatory sensitivity and the development of symptoms of hypercapnia in the water during exercise under the main part of the protocol of which this work is a part.<sup>4</sup>

## DISCUSSION

In a five individuals, ventilatory sensitivity increased markedly with one or more of the added resistances (Figure 2a). In two, it was severely depressed (Figure 2), either overall or until  $\text{PCO}_2$  was considerably elevated. However, resting ventilatory sensitivity to  $\text{CO}_2$  did not decrease on the average or consistently when resistance was added to the breathing the circuit. This is contrary to predictions of the dual control model of ventilatory control in which a combined function of the chemoreceptor “error” signal and a work of breathing signal drives minute ventilation.<sup>1</sup> Other evidence supports that model.,<sup>14, 15, 19, 20</sup> Discussion follows of factors that differentiate between those measurements and resting ventilatory sensitivity measurements.

The rebreathing method (and our current in-water exposures) involves high oxygen partial pressures. Hyperoxia almost silences the peripheral chemoreceptors and damps the central chemoreceptor response to  $\text{CO}_2$ .<sup>26</sup> We have seen that it also damps exercise ventilation,<sup>2, 3</sup> perhaps through the same mechanism. It is possible that hyperbaric hyperoxia further decreases chemical sensitivity to  $\text{CO}_2$ .

Read’s rebreathing method provides a sudden large step change in  $\text{PCO}_2$ , while the ventilatory control system normally deals with small chemical “error” signals. The strength of the chemical signal during the rebreathing maneuver may be sufficient to overcome any small ventilatory effort feedback. Read’s rebreathing method also provides a constant increase in  $\text{PCO}_2$  independent of the strength of the ventilatory response; the respiratory controller may have an additional sensitivity to the rate and direction of change of  $\text{PCO}_2$ , a sensitivity not accounted for in the model developed for other conditions.<sup>1</sup> Measurements with more moderate steady state elevations in  $\text{PCO}_2$  have shown evidence of resistance effects at rest.<sup>14, 20</sup>

Work of breathing was not totally without effect on ventilatory sensitivity in our experiments, but the effects were noticeable only when  $\dot{V}_E$  was very high. Our resistance was moderate; the pressure drop in the rebreathing circuit at peak flow of 100 L/min approximately doubled with one resistive element and tripled with two, but the work of breathing at  $\dot{V}_E = 100$  L/min, approximately 1 kPa for a single resistor or 2 kPa with both, was within the acceptable range for breathing gear.<sup>27</sup> Other investigators saw decreased ventilatory response to  $\text{CO}_2$  with resistance,<sup>21</sup> but they used only very high resistance and thus always saw an effect on ventilation; the resistance they used was sufficient to reduce maximum voluntary ventilation by up to a factor of four. However, this study was not designed to investigate the effects of a physical upper limit on ventilation. The question we asked was whether moderate resistance changes the apparent chemoreceptor response, and the answer is that it does not.

By design, each condition was measured once per person. We rely on the literature for measures of reproducibility. Other investigators have reported coefficients of variation (CV) for an individual ranging from 2.0 to 15%, mean 5.8% after 220 tests on 42

subjects, with the differences between any two tests rarely exceeding two standard deviations.<sup>25</sup> Longer term CVs from multiple tests over different days ranged from 2.0 to 8.4%, with a mean long-term CV of 5.6%.<sup>27</sup> With these values, simple retest variability could cause an apparent transition from 1 (“expected”) to 0.77 (“low”) or from 0.99 (“low”) to 1.22 (“expected”). Results from tests of 12 men three times each in another laboratory found the average CV to be 15%.<sup>25</sup> However, not even high retest variability easily accounts for either the three-fold increase of initial sensitivity in two individuals or the absence of response either for all PCO<sub>2</sub> or until PCO<sub>2</sub> was extremely high, in another two.

The technical quality of the traces of PCO<sub>2</sub> vs. time generally were good for the responsive and non-responsive subjects alike, though PCO<sub>2</sub> at the end of 4 minutes was relatively low (<60 Torr) for some of the non- or late responses. A sampling of the files shows a rise of PCO<sub>2</sub> with time after bag mixing of 0.6 to 0.9 kPa/min, comparable with Read’s mean slope of 0.8 kPa/min, and an initial rise in end tidal PCO<sub>2</sub> of 0.9 to 2.3 kPa, comparable to that of about 1.2 kPa estimated from Read’s values.<sup>17</sup> A plateau in PCO<sub>2</sub> could be observed briefly after gas mixing.<sup>16</sup> Although a total of five of the 64 measurements showed poor mixing and absence of initial plateau, those all yielded ventilatory sensitivities in the expected range.

Published values for responses in healthy people range from 0.6 to 8.2 (L/min)/Torr in a distribution that is skewed towards the lower part of that range; 80% of the healthy population has a response between 1 and 4 (L/min)/Torr.<sup>16</sup> In this small sample of divers, without added resistance 69% of individuals showed ventilatory sensitivities to CO<sub>2</sub> in the expected range between 1 and 4 (L/min)/Torr. This proportion is not different from 80% by Fisher’s Exact test, with  $p > 0.2$  when compared to hypothetical control populations of size 100 to 100,000. Although a number of authors have suggested that divers are less sensitive as a group than are non-divers, some of the conclusions may be based on statistical tests that implicitly assume that sensitivities to CO<sub>2</sub> are normally distributed, though the distribution highly skewed<sup>16</sup> and at least approximately log-normal (Figures 3 and 4).

This is a study of men only. Ventilatory response of women to CO<sub>2</sub> has been reported as lower than that of men when measured by rebreathing<sup>28, 29</sup> or higher than that of men when measured using steady state methods.<sup>30</sup> The effect of resistance on chemical control in women is unknown.

Regardless of the effects of resistance, the near absence of ventilatory sensitivity to CO<sub>2</sub> in the water while breathing hyperoxic gas represents a major risk for a diver. That a diver in the water might breathe at or barely above normal resting  $\dot{V}_E$  (about 12 L/min) while his PCO<sub>2</sub> was 60 Torr (Figures 4, 5) (normal resting arterial PCO<sub>2</sub> = 40 ± 2 Torr) would preclude his breathing down the high CO<sub>2</sub> and put him at risk of central nervous system oxygen toxicity and hypercapnic symptoms. If in-water and dry resting responses were related, the dry measurements would provide an easy test of diver risk; lack of ventilatory sensitivity to CO<sub>2</sub> could be used as a possible disqualifying characteristic for diving with oxygen rebreathers.

Some investigators have found that the rebreathing measurement of ventilatory sensitivity to CO<sub>2</sub> during hyperoxia yields slopes that are higher than those found with steady-state exposure to CO<sub>2</sub> with hyperoxia.<sup>31</sup> Although the assumption of Read's rebreathing method is that the PCO<sub>2</sub> at the central chemoreceptors is the same as that in arterial blood,<sup>17</sup> those investigators have pointed out that tissue PCO<sub>2</sub> is somewhat higher than arterial PCO<sub>2</sub>; the ventilatory response is, in fact, to a higher PCO<sub>2</sub> than that measured. The implication is that the rebreathing method overestimates the ventilatory response of longer-term exposure to elevated CO<sub>2</sub>, exposure more like that of exercise experiments. In other words, ventilatory sensitivity to CO<sub>2</sub> in the water is likely to be **lower** for some of these divers than the response we measured in these experiments. For the measurements to be equal, it may be necessary to have the initial step in PCO<sub>2</sub> at 0.5 kPa<sup>32</sup> rather than the 1.2 kPa that is typical of Read's method.<sup>31</sup>

Unfortunately for safety screening of divers, there is no relationship between dry resting ventilatory sensitivity to CO<sub>2</sub> and proclivity to retain CO<sub>2</sub> during exercise underwater. (The in-water results will be reported in detail elsewhere.) At least one diver in this series who had resting ventilatory sensitivity in the expected range on land reached very high end tidal PCO<sub>2</sub> during exercise in the water, and a number of other divers with normal sensitivity experienced symptoms of hypercapnia in the water — headache, nausea, anxiety, dizziness, and inability to remember instructions. Although the two divers who showed initial lack of ventilatory response to CO<sub>2</sub> with resistance were among those whose end tidal PCO<sub>2</sub> reached 65 Torr during underwater exercise, another diver whose PCO<sub>2</sub> reached that level showed expected ventilatory sensitivity for all resistance conditions.

Different measures of ventilatory sensitivity to CO<sub>2</sub> may stimulate differently and thus yield differing results.<sup>31,32</sup> One study that found ventilatory sensitivity to CO<sub>2</sub> correlated with the increase in minute ventilation during exercise also measured ventilatory sensitivity to CO<sub>2</sub> during exercise, and only with a slow increase in PCO<sub>2</sub>.<sup>19</sup> The authors did not compare ventilatory sensitivity during exercise to that at rest. Other investigators who measured ventilatory sensitivity at rest using Read's method as we did also found no correlation between the resting measurements and those during exercise.<sup>18</sup>

Ventilatory sensitivity to and awareness of elevated PCO<sub>2</sub> are different issues, and awareness may be the critical safety factor. Indeed, divers can be trained to recognize symptoms of hypercapnia.<sup>33</sup> Although those with very low ventilatory sensitivity would not experience air hunger or hyperpnea, other symptoms that could be highlighted during training might be sufficient to enhance diver safety. In our group of subjects, one diver with very low ventilatory sensitivity and a very high PCO<sub>2</sub> was aware of his symptoms when his PCO<sub>2</sub> became very high during a dive and stopped exercise voluntarily. He could probably be trained to recognize his symptoms earlier. However, two divers who reached similar elevated PCO<sub>2</sub> were unaware of any problem during testing and could be considered to be at risk when they dive.



## **CONCLUSIONS**

Moderate resistance does not appear to change resting ventilatory response to CO<sub>2</sub> in any significant or systematic way. For a few individuals, ventilatory response to CO<sub>2</sub> is abolished in the presence of resistance in the breathing circuit, and for a few, it increases when breathing is more difficult. The dual control model that CO<sub>2</sub> and breathing effort together determine the output of the respiratory controller is clearly incomplete.

Recognition of the non-normal distribution of ventilatory sensitivity to CO<sub>2</sub><sup>16</sup> is important for hypothesis testing about populations and sensitivity.

The increase of ventilation with exercise is a composite response of the exercise response itself, possible chemoreceptor correction, and potentially other control mechanisms.<sup>34</sup> The resting ventilatory response to rebreathing uses fast changes in PCO<sub>2</sub> to stress aspects of ventilatory control that are possible not involved in the exercise response. Thus, a lack of consistent relationship between resting and exercise sensitivities is not surprising.

Ultimately, the absence of connection between ventilatory sensitivity to CO<sub>2</sub> at rest and during exercise reduces the importance of measurements of resting ventilatory sensitivity to CO<sub>2</sub> in divers. Instead, it emphasizes the importance for safety of testing during underwater exercise.

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